REMARKS

Claims 1-11 are pending and at issue. Claim 1 has been amended to recite that the bisphosphonate provides prolonged pain relief. Support for the claim 1 amendment can be found in the specification at, for example, page 7, lines 11-14 and page 8, line 1 to page 8, line 10.

The obviousness rejections

(1) Claims 1-9 and 11 have been rejected as obvious over Geusens et al., J of Clin Densitometry, 2001;4:389-394 ("Geusens"). According to the Examiner, Geusens discloses the case history of an 18-year old boy treated with intravenous pamidronate (a bisphosphonate) for extreme back pain resulting from multiple vertebral fractures. The pamidronate was administered intermittently over a nine month period. The patient's back pain progressively improved. *See,* Office Action, page 3.

The Examiner acknowledges that Geusens does not teach treating chronic spinal mechanical pain, i.e., any back pain lasting more than twelve weeks which is not caused by cancer or an osteoporotic compression fracture. However, the Examiner contends that it would have been obvious to use pamidronate for the treatment of any back pain because Geusens discloses the effectiveness of pamidronate in pain management. *Id.* at 3-4.

Applicant respectfully traverses this rejection. The claims as amended recite that the biophosphonate provides "prolonged pain relief." The specification defines "prolonged pain relief" to mean "relief from chronic mechanical pain for a duration of more than one month, preferably for 3 months, and more preferably for 6 months." Specification, page 7, lines 12-14. This feature is unexpected and rebuts the *prima facie* obviousness rejection. As disclosed in the specification, the instant invention includes the discovery that: "administering an effective amount of bisphosphonate intravenously to a subject in need of pain relief from chronic spinal mechanical pain results in the subject experiencing prolonged pain relief, going well beyond the period in which the analgesic properties of bisphosphonates ... are known to be effective." Specification, page 6, line 18 to page 7, line 1. Data supporting this unexpected result is provided in the Example, which reports that three subjects suffering from chronic spinal mechanical pain were pain free at 1, 2, 4, and 6 months

following their last dose of intravenous pamidronate. *See,* specification, page 8, line 1 to page 9, line 10.

The specification discloses a clinical study of three subjects suffering from chronic spinal mechanical pain for greater than one year. Each subject was intravenously administered about 1.2 mg/kg of pamidronate once a day for three days. At baseline, Subject 1 rated her pain as 8 on a 1-10 scale (0 = no pain, 10 = worst pain imaginable), subject 2 rated her pain as 8-9, and Subject 3 rated her pain as 5. At one month following pamidronate therapy, Subjects 1-3 rated their pain as 4, 5, and 0, respectively. At 2, 4 and 6 months post-pamidronate therapy all Subjects reported no pain, i.e., a 0 on the scale. *Id.* Some subjects took non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen sporadically during the post-pamidronate period. However, the prolonged pain relief can be attributed to the intravenous pamidronate therapy because the analgesic effect of NSAIDs and acetaminophen is known to last only a few hours. *Id.*

Geusens does not disclose or suggest that a bisphosphonate can provide such long term pain relief. Geusens does not expressly state that the patient's pain improved as a result of pamidronate treatment. The patient described in Geusens received calcitonin, analgesics, and non-steroidal anti-inflammatory drugs to treat his pain. The patient was also started on physiotherapy and progressive mobilization. Geusens does expressly state that pamidronate was administered to improve bone density. Further, alleviating pain is not an inherent feature of treating low bone density (osteoporosis) because patients with osteoporosis do not necessarily have chronic spinal mechanical pain.

Geusens poses the question: "How long should bisphosphonates be given?" Geusens, page 393, right column. Thus, Geusens does not disclose or suggest that, when used to treat pain, bisphosphonates have a prolonged effect, i.e., an effect that lasts well beyond the last dose, does not require chronic administration, and can even cure chronic pain. The instant invention includes these unexpected features. *See*, specification, page 5, lines 1-7.

Accordingly, for the reasons stated above, this rejection should be withdrawn.

(2) The Examiner has rejected claims 1-8, 10 and 11 as obvious over Urban et al., Society for Neuroscience Abstracts, 2001;27(1):1326 ("Urban") in view of U.S. Patent No.

6,676,970 ("Bader"). According to the Examiner, Urban discloses that zoledronate (a bisphosphonate) produces an anti-allodynic effect in rats, and Bader discloses parental zoledronate preparations. The Examiner contends that one of ordinary skill in the art would have been motivated to use intravenous zoledronate to treat pain as an alternative to the subcutaneous formulation disclosed in Urban. *See,* Office Action, pages 4-5.

Applicant respectfully traverses this rejection. Urban discloses a study of rats injected intra-tibially with cancer cells. The rats developed allodynia (a condition in which ordinarily nonpainful stimuli evoke pain, *see* Stedman's Medical Dictionary, 26th ed. 1995, copy attached) and hyperalgesia. According to Urban, subcutaneous zoledronate produced an anti-allodynic effect in the rats. Urban suggests that: "[z]oledronate ... has therapeutic potential in bone cancer attenuated allodynia and hyperalgesia in the model." Urban does not disclose or suggest that zoledronate has an effect on typical, non-allodynic pain, much less an effect on chronic spinal mechanical pain. Bader does not disclose or suggest the treatment of pain with a bisphosphonate.

Further, no combination of the references discloses or suggests that a bisphosphonate provides prolonged pain relief. As discussed in greater detail above, the instant specification discloses that subjects suffering from chronic spinal mechanical pain received prolonged pain relief following intravenous pamidronate therapy. *See,* specification, page 8, line 1 to page 9, line 10. Thus, this *prima facie* rejection is rebutted by the unexpected result of the present invention that a bisphosphonate provides prolonged relief of chronic spinal mechanical pain.

Accordingly, the amended claims are non-obvious and this rejection should be withdrawn.

Conclusion

In view of the above remarks, it is respectfully requested that the pending claims be allowed and the case passed to issue.

If there are any other issues remaining, which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully

requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

By _____

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